March 4, 2005

Ken Nitschke
Technical Contact
Dow Chemical Company
1691 North Swede
Midland, MI 48674

Dear Mr. Nitschke:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Commercial Hydroxyethylpiperazine, posted on the ChemRTK HPV Challenge Program Web site on February 24, 2004. I commend Dow Chemical Company for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Dow advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Acting Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/S/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Commercial Hydroxyethylpiperazine

Summary of EPA Comments

The sponsor, The Dow Chemical Company, submitted a test plan and robust summaries to EPA for Commercial Hydroxyethylpiperazine (Commercial HEP) dated December 23, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 24, 2004. Commercial HEP contains 38-47% hydroxyethylpiperazine (HEP, CAS No. 103-76-4), 16-25% dihydroxyethylpiperazine (DHEP, CAS No. 122-96-3), 12-20% piperazine (PIP, CAS No. 110-85-0), and 17-26% water as impurities.

EPA has reviewed this submission and has reached the following conclusions:

1. Physicochemical Properties. The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

2. Environmental Fate. The submitter needs to provide 28-day ready biodegradation data for HEP and DHEP and add information to several robust summaries.

3. Health Effects. The submitted acute toxicity data on Commercial HEP are adequate for the purposes of the HPV Challenge Program. EPA concurs with the submitter's plan to conduct a chromosomal aberrations test and a reproductive/developmental toxicity screening test on Commercial HEP. Data are also needed to address the gene mutation endpoint on Commercial HEP. Because repeated-dose toxicity data are inadequate on Commercial HEP, and the submission did not adequately support the closed system intermediate reduced-testing claim for the chemical, the submitter needs to address all health effects endpoints; EPA recommends including the repeated-dose toxicity test with the combined reproductive/developmental toxicity screening test.

4. Ecological Effects. EPA agrees that adequate data are available for fish, invertebrate, and alga toxicity for the purposes of the HPV Challenge Program. However, the submitter needs to provide some missing data elements in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA Comments on the Commercial Hydroxyethylpiperazine Challenge Submission

General

In the test plan introduction (p. 4/18), three different names are used for DHEP in different places. Only "bis(hydroxyethyl)piperazine" is strictly correct; consistent usage and the addition of a structural diagram would eliminate confusion.

The submitter's claim that Commercial HEP meets the EPA definition of a closed system intermediate was not substantiated with adequate information.

Data for PIP are presented as a draft EU risk assessment document; the submitter indicated that a robust dossier for PIP will be prepared by the Swedish authorities in the near future and will be added to the data package when available. EPA did not review the risk assessment document.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility)

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

Photodegradation. The data provided by the submitter for HEP and DHEP are adequate for the purposes of the HPV Challenge Program. The submitter needs to incorporate in the piperazine robust summary the estimated half-life recorded in table 2 of the test plan.

Stability in water. While EPA agrees that these chemicals are not susceptible to hydrolysis, the submitter needs to explain the point briefly in the robust summary for each chemical.

Biodegradation. The biodegradation studies submitted for HEP and DHEP are not adequate for the purposes of the HPV Challenge Program. The submitted data for both chemicals are inconclusive since the test duration was only 20 days and little biodegradation was observed. The submitter needs to provide 28-day ready biodegradation data for both substances following OECD TG 301.

Fugacity. The data provided by the submitter for HEP and DHEP are adequate for the purposes of the HPV Challenge Program. The submitter needs to incorporate in the robust summary the level III fugacity information for piperazine recorded in table 2 of the test plan and the input values used.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Commercial HEP is a complex mixture in which no one component predominates; therefore, the health effects assessment of an individual component does not adequately characterize the potential health effects of the mixture. EPA agrees with the submitter that testing is needed on Commercial HEP to address the reproductive/developmental toxicity and chromosomal aberration endpoints. In addition, the submitter needs to provide gene mutation data on Commercial HEP.

The submitted data for acute toxicity are adequate for the purposes of the HPV Challenge Program.

Repeated-Dose Toxicity. The submitted data for repeated-dose toxicity of Commercial HEP are inadequate (7-day study duration). Potentially adequate data for >99% pure PIP (submitted as a draft EU Risk Assessment) will not adequately characterize Commercial HEP. The submitter claims that Commercial HEP meets the EPA definition of a closed system intermediate (CSI) and has not proposed repeated-dose toxicity testing.

The "Guidance for Testing Closed System Intermediates" for the Challenge Program at http://www.epa.gov/chemrtk/guidocs.htm allows for a reduced testing protocol provided certain criteria are met. The information required to support a CSI claim must address the following:

I. Site information
    A. Number of sites.
    B. Basis for "closed process" conclusion at each site.
        1) Process description.
        2) Monitoring data showing no detection.
        3) In the absence of monitoring data, the basis for believing that releases do not occur.
    C. Data on "presence in distributed products."

II. Information on transport (mode, volume, controls, etc)
III. A data search showing that the chemical is not present in other end products.

EPA believes that the submitted information is inadequate to satisfy the requirements for classification of Commercial HEP as a CSI eligible for reduced testing in the HPV Challenge Program for the following reasons:

IA. *Number of sites*. The subject chemical is manufactured at several sites in the U.S. other than those of the submitter and information is not provided on the manufacture, processing, and use of the subject chemical at the other sites.

IB (1). *Process description at each site*. The equipment used to manufacture, process, and store or consume the subject chemical is not described.

IB (2) (3) and IC. *Monitoring data, if available, showing no detection in any media.* The test plan does not provide either monitoring data on releases from process units or, in the absence of data, a reason for believing there is no release of the chemical from any process unit. The test plan states "Based on the uses of Commercial HEP, exposure to this product will be very limited and is only expected to occur in manufacturing sites of HEP or TEDA." Release of the chemical and exposure to Commercial HEP during use for removal of acid gases from natural gas streams are not discussed. In the absence of a process description and reasons for believing no release of the chemical occurs, the information submitted is inadequate.

II. *Information on transport*. The test plan states that "the product is shipped as Commercial HEP." Movement of the chemical between sites is not described in the test plan and neither is any assurance provided that there is no release of the subject chemical nor exposure of personnel during transport of the chemical. Equipment for transferring and storing Commercial HEP is not described.

III. *A data search showing that the chemical is not present in other end products*. The test plan states that "Residual levels of Commercial HEP could be present in TEDA. However, the levels of the components of Commercial HEP would be quite low." This appears to contradict the requirement that the closed system intermediate not be present in distributed products at levels above trace concentrations.

The test plan states "The Dow Chemical Company is unaware of Commercial HEP being sold into consumer applications in the US." The subject chemical could, nevertheless, be present in industrial or commercial products, or could be an impurity or unreacted intermediate in distributed products that are not managed in closed systems. In addition, the test plan does not provide information on all manufacturers of HEP.

Unless adequate additional information is provided to support the CSI claim, the submitter needs to address all health effects endpoints for the purposes of the HPV Challenge Program (see below under *Reproductive/Developmental Toxicity).*

Genetic Toxicity. No gene mutation data were submitted for Commercial HEP. Therefore, the submitter needs to provide a gene mutation assay (OECD TG 471) on Commercial HEP.

EPA agrees with the submitter's proposal to conduct an *in vitro* chromosomal aberration test on Commercial HEP according to OECD TG 473.

Reproductive/Developmental Toxicity. EPA agrees with the submitter's proposal to conduct combined testing of Commercial HEP according to OECD TG 421 to address the reproductive and developmental endpoints. If the submitter's CSI claim remains unsupported, EPA recommends that the submitter conduct a combined repeated dose/reproductive/developmental toxicity screening test according to OECD TG 422 in order to satisfy all the health effects data needs.

Ecological Effects (fish, invertebrates, and algae)

EPA agrees that adequate data are available for fish, invertebrates, and alga toxicity for the purposes of the HPV Challenge Program. However, the submitter needs to add some missing data elements to the robust summaries.

Specific Comments on the Robust Summaries

Health Effects

Genetic Toxicity. Missing study details from the robust summary submitted for a bacterial reverse mutation assay on HEP include concentrations tested, number of replicates per concentration, culture conditions, control use and response, statistical methodology, evidence that the study included a cytotoxic concentration, and results of the study.

Missing study details from the robust summary for a bacterial reverse mutation assay on DHEP include the number of replicates per concentration, culture conditions, and statistical methodology.

Ecological Effects

Fish. The submitter needs to provide a robust summary for PIP when it becomes available and include the following data elements in the robust summary: control use and response, number of replicates per concentration, loading rate of the fish, dissolved oxygen measurements, water hardness values, TOC, and statistical methods used. The submitter also needs to report whether analytical monitoring was performed.

Invertebrates. The robust summary submitted for acute toxicity of daphnia to HEP was missing study details such as TOC, temperature, and statistical methods used. It did not report whether analytical monitoring was performed. Clarification is needed on the identity of the test substance because the summary identifies the test substance as Commercial HEP, while Table 3 in the test plan shows the data for HEP itself and states “no data” for Commercial HEP.

The robust summary submitted for acute toxicity of daphnia to DHEP was missing study details such as test substance identity and purity, TOC, temperature, and statistical methods used.

The submitter needs to provide a robust summary for PIP when it becomes available and include the following data elements in the robust summary: control use and response, the age and loading rate of the daphnids, signs of toxicity/mortality per dose, dissolved oxygen measurements, TOC, and water hardness values. The submitter also needs to report whether analytical monitoring was performed.

Similarly, the new robust summary for the PIP *chronic toxicity* study of daphnia needs to include the following study details: test substance purity, control and dose response, the age of the daphnids, number of brood neonates, dissolved oxygen measurements, TOC, and water hardness values.

Algae. The new robust summary on PIP needs to include the following study details: control use and response, lighting conditions, and initial cell concentration. The submitter also needs to report whether analytical monitoring was performed.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.